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Case Report

Human Herpesvirus-6 (HHV-6)–Associated Necrotizing Encephalitis in Griscelli's Syndrome

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We report a male caucasian German pediatric patient of no Arab or Mediterranean ancestry with virus associated CNS lesions in Griscelli's syndrome (GS; McKusick No. 214450). The boy presented with recurrent infections, and meningitis with subsequent progressive signs of increased intracranial pressure leading to death at 32 weeks of age. At autopsy, various sites of the CNS revealed necroses in gray and white matter. CNS histology revealed numerous and massive predominantly perivascular CD8 positive lymphohistiocytic infiltrates. These findings were associated strictly with the presence of human herpesvirus-6 (HHV-6) genome or the HHV-6 specific late antigen H-AR 3, found in neurons, oligodendrocytes, and astrocytes. The search for HHV-6 replication dependent antigen, HHV-7 DNA, CMV, adenovirus, Coxsackie B1, B2, and B4-antigens, and mycobacteria was not successful. Detection of viruses was attempted using immunohistochemistry, in situ hybridization or nested polymerase chain reaction, respectively. Lymphocyte typing was carried out immunohistochemically. In GS, virus induced CNS damage does not seem to require necessarily active virus replication. It may also appear as a consequence of an immune reaction triggered by antigen expression. ***J. Med. Virol. 53:306–312, 1997.***

KEY WORDS: central nervous system; cytotoxic T-cells; McKusick no. 214450; ethnic background

INTRODUCTION

Griscelli's syndrome (or GS, Griscelli-Prunieras syndrome, Griscelli-Prunieras disease, GPD, Chediak-Higashi-like syndrome, partial albinism with immunodeficiency, PAID syndrome, syndrome of pigmentary dilution and lymphohistiocytosis, silvery hair syndrome; McKusick No. 214450) [McKusick, 1990] is a rare and probably autosomal recessive hereditary disease consisting mainly of immunodeficiency with pigmentary dilution [Griscelli et al., 1978]. All GS patients reported of so far are of Arab or Mediterranean ancestry. Cerebral involvement has been described as lymphohistiocytic infiltration with necroses. Some authors suggest that these changes may be due to an autoimmune reaction or a low virulent infection, but viral involvement has never been demonstrated.

CASE REPORT

We report the case of a single male child of consanguinous Caucasian Germans of no Arab or Mediterranean ancestry but with identical great-grandparents. Pregnancy and birth were uneventful. From birth on (as opposed to prematurely) the patient's hair (capillitium and eyebrows) had a silvery sheen as described for GS [Griscelli et al., 1978; Durandy et al., 1993; Kanitakis et al., 1991; Klein et al., 1994]. There was neither ocular nor cutaneous hypopigmentation. After 7 uneventful weeks he was hospitalized because of fever and vomiting. On physical examination he appeared pale and had hepatosplenomegaly. Laboratory investigations revealed anemia (4.0 g/dl), neutropenia (250/μl), and thrombocytopenia (8000/μl), and signs of an infectious disease. Differential diagnosis of GS was carried out excluding Chediak-Higashi syndrome (CHS, Steinbrinck-Chediak-Higashi syndrome, SCH,

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Beguez-Chediak-Higashi syndrome, BCH) [Durandy et al., 1993; Kanitakis, et al., 1991], Elejalde disease (ED, Elejalde syndrome, neuroectodermal melanolysosomal disease, NEMLD) [Elejalde et al., 1979], Cross syndrome (oculocerebral-hypopigmentation syndrome) [Cross et al., 1967], Ozand syndrome (Riyadh chromosome breakage syndrome) [Ozand et al., 1992], Hermansky-Pudlak syndrome (albinism with haemorrhagic diathesis) [Lattion, et al., 1983], ataxia telangiectasia [Waldmann et al., 1982], Vici syndrome [Vici et al., 1988], and Morbus Farquhar (familial hemophagocytic syndrome, FHS, familial hemophagocytic reticulosis, FHR, familial hemophagocytic lymphohistiocytosis, FHLH) [McClure et al., 1974]. He received transfusion of erythrocytes and platelets, and antibiotic therapy was started. The further course was characterized by progressive hepatic failure with hyperfibrinolysis. On admission the child did not have neurological signs. He was jittery but otherwise behaved normally. With hepatic failure he developed encephalopathy and generalized tonic-clonic seizures. EEG showed a burst-suppression pattern with no discernible focal activity. There was no evidence of meningitis or intracerebral pathology. Due to uncorrectable thrombocytopenia with bleeding by the age of 8.5 weeks, splenectomy accompanied by a liver biopsy was carried out. The patient's clinical and neurological status improved after splenectomy and he was discharged at 11.5 weeks of age. His blood count was normal. At age 14.5 weeks he was readmitted because of meningitis (CSF cell count: 110/3) followed by pneumonia at the age of 16 weeks. Again thrombocytopenia, neutropenia, and coagulopathy developed. Progressive signs of increased intracranial pressure appeared at age 17 weeks: he had papilledema. At age 18 weeks the patient was microcephalic. On sonographic examination of the brain, enlargement of the lateral ventricles was noted. The child's condition deteriorated despite antibiotic and antimycotic therapy, dexamethasone, and acetazolamide. At the age of 23 weeks he was obtundated, did not fixate and had a developmental delay of more than 12 weeks. Recurrent infections complicated the further course, and neurological condition progressed to coma. Sonographic examination at the same time showed increased echodensity of the hemispheres and further enlargement of the lateral ventricles. The child died at 32 weeks of age.

METHODS

Lymphocyte typing was carried out immunohistochemically using monoclonal antibodies to OPD4, CD8, CD45RO (UCHL), and CD20 (L 26; all antibodies by DAKO, Denmark) using the alkaline phosphatase anti-alkaline phosphatase (APAAP) technique or streptavidin-biotin complex (ABC) method. Monoclonal antibodies to human glial fibrillary acidic protein (GFAP; DAKO, Denmark; APAAP technique) were used to identify glial cells immunohistochemically.

Detection of HHV-6 was also attempted immunohistochemically. Monoclonal antibodies were applied to the HHV-6 replication dependent late early antigen p41 (9A5D12, D12; APAAP method on tissue of the liver and ABC method on liver and brain). A HHV-6 specific late antigen, the glycoprotein gp 110/60 (H-AR 3), was searched for using the APAAP technique with monoclonal antibodies. In situ hybridization (ISH) to detect HHV-6 DNA was performed using the non-cross-reactive biotinylated probes pZVB70 and pZVH14 [Josephs et al., 1986]. Furthermore, nested polymerase chain reactions (nPCR) for HHV-6 and human herpesvirus-7 (HHV-7) DNA were carried out using the following primers. 1) for HHV-6 detection: P0 (external; sense), P4 (external; antisense), P1 (internal; sense), and P3 (internal; antisense) and 2) for HHV-7 detection: HV7 and HV10 (sense), and HV8 and HV11 (antisense) [Klotman et al., 1993]. Immunohistochemistry (IHC using monoclonal antibodies, ABC method) was performed to exclude other virus infections known to cause similar histological patterns in the brain (CMV: DAKO, Denmark; adenovirus, Coxsackie B1, B2, and B4: Biogenesis, England). Ziehl-Neelsen's staining was used when searching for mycobacteria.

RESULTS

Histologically, the liver presented portal and (focally) intralobular lymphohistiocytic infiltration. In situ hybridization (ISH) and immunohistochemistry (IHC) were positive scantily for HHV-6 DNA and p41 in proliferating biliary duct epithelia. The majority of the lymphocytic fraction of the infiltrate consisted of CD8-positive and CD45RO-positive T-cells; only a few were OPD4-positive. Light microscopic examination of the hair revealed large clumps of pigment within the hair shafts and increased diameter of the hair as compared to the hair shafts of a healthy fair-haired child. CD20-positive B-lymphocytes were absent in the liver but abundant in the spleen.

The parents permitted autopsy only of the brain (weight, 585 g; normal would be 700 g). The abdomen and thorax of the 8-month-old icteric infant (length, 59 cm; weight, 5.250 g; normal would be 70 cm and 8500 g) were not examined. Petechia were seen on trunk, thighs, and upper arms. Frontal slices of the brain disclosed an enlargement of the lateral ventricles as well as numerous focal necroses, each between 0.5 cm and 1.5 cm in diameter. Necroses located in the gray matter were mostly hemorrhagic, whereas the majority of necroses in the white matter were reminiscent of edematous necroses (Fig. 1). Histologic examination revealed diffuse necroses of the latter and selective neuronal necroses. Both were found in all cerebral lobes, basal ganglia, diencephalon, brain stem, cerebellum, and down to the cutoff in the C1 segment of the spinal cord. In all the locations (as well as in the optic nerve and the anterior and posterior pituitary lobe) a massive lymphohistiocytic infiltration could be seen in leptomeninx, gray, and white matter (Fig. 2a–c). Focal infiltrates were predominantly situated at the pial-cortical junction and showed a granuloma-like perivascular pattern ("perivascular cuffs"). A more diffuse infiltrate

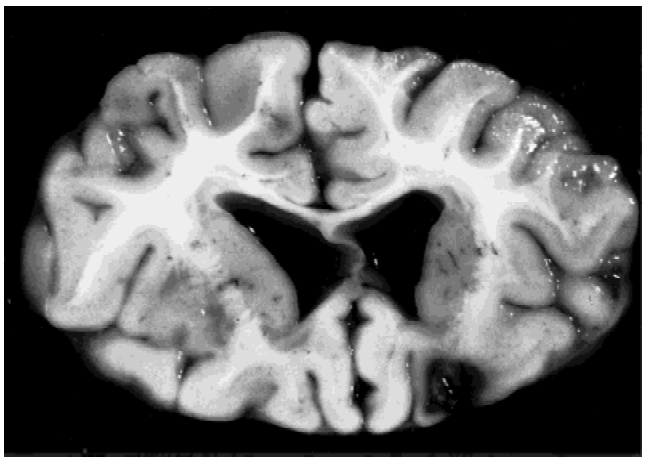

Fig. 1. Frontal slices of the brain showing hemorrhagic necrosis of gray matter (right), necroses-associated dyscoloration of white matter (left), and enlargement of the lateral ventricles.

was found in the brain parenchyma. The lymphocytes (often in a karyorrhectic state) were predominantly CD8-positive and CD45RO-positive with OPD4-positive cells situated in necroses. CD20-positive B-lymphocytes were almost completely absent. Histiocytes occured in the form of rod cells in perivascular granuloma-like nodules and as typical lipid containing scavenger cells. Massive perivascular cuffs were often not associated with destruction, whereas more diffuse infiltrates were often associated with extensive necrotization. Anti-H-AR 3 staining, ISH (Fig. 3), and nPCR for HHV-6 DNA were positive, although IHC using monoclonal antibodies to p41-antigen was negative. H-AR 3 was found in neurons, oligodendrocytes, and astrocytes. All necroses and lymphocytic infiltrates examined were strictly associated with areas positive for HHV-6. Demyelination (as often described for GS radiologically) was not seen. All attempts (ISH, nPCR) to detect HHV-7 failed, and IHC for CMV, adenovirus, and Coxsackie B1, B2, and B4 antigens, as well as an intensive search for mycobacteria, showed negative results. Chloracetatesterase staining (for detection of monomyeloic cells) was uneventful.

Summarizing the neuropathologic findings, there was an atypical lymphohistiocytic infiltration with numerous necroses of a panencephalitic type.

DISCUSSION

All patients reported so far to have GS are of Arab or Mediterranean ancestry. The disease is known to present with so-called accelerated phases [Kanitakis et al., 1991], which perhaps are associated with virus infections [Klein et al., 1994]. GS may be seen as an autosomal recessive and chronic progressive disease [Griscelli et al., 1978] with maybe a widespread cell membrane defect responsible for most symptoms known so far [Brambilla et al., 1980].

In GS, cerebral involvement is known to be a progressive alteration to white matter (onset: infancy) with diffuse or focal lymphohistiocytic infiltration with

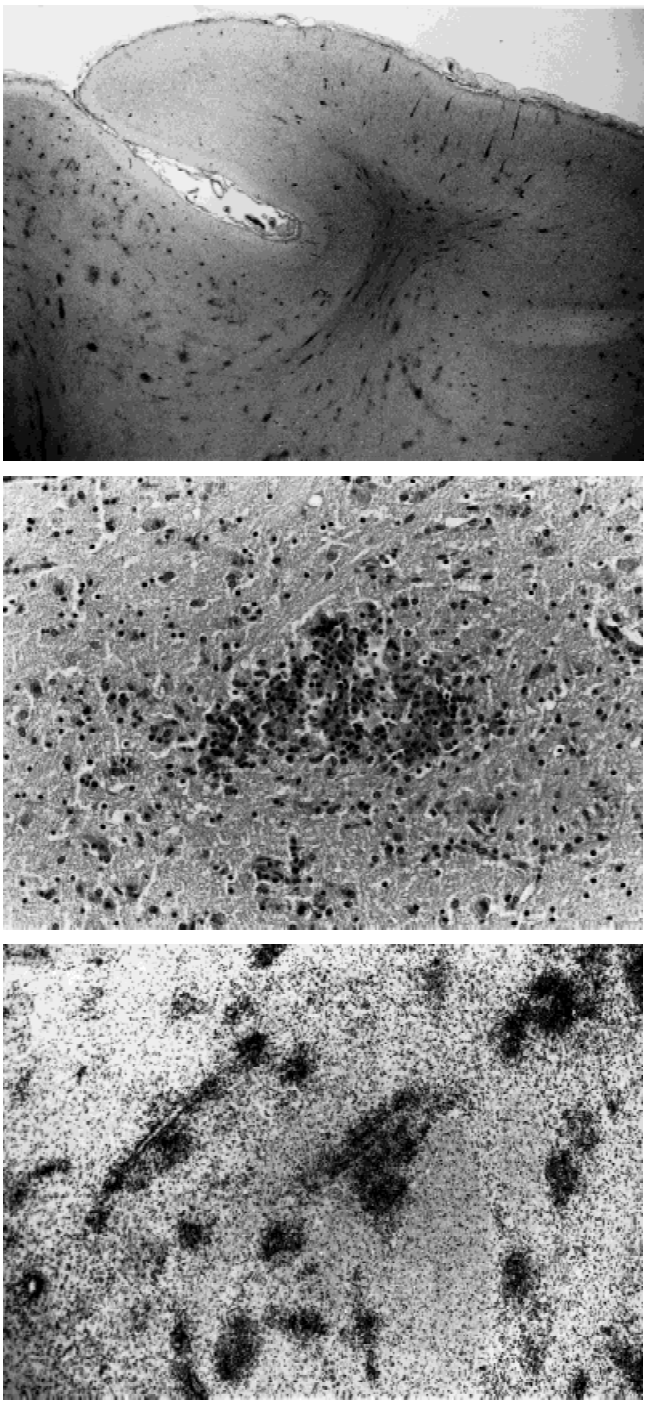

Fig. 2. **a:** Perivascularly and subpially accentuated distribution of inflammatory cells, (HE; 10×). **b:** Circumscribed granuloma-like histiocytic accumulation in thalamus with preserved neuronal and glial structures (HE; 250×). **c:** Predominant perivascular T-lymphocyte spreading in the pons: "perivascular cuffs" (UCHL; 65×).

erythrophagocytosis and eventual loss of brain tissue [Schneider et al., 1990; Haraldsson et al. 1991; Brismar and Harfi, 1992; Harfi et al., 1992]. A recent publication reports cases with (not further specified) lymphocytes prominent around blood vessels and a diffuse distribution of histiocytes in the parenchyma [Gögüs et

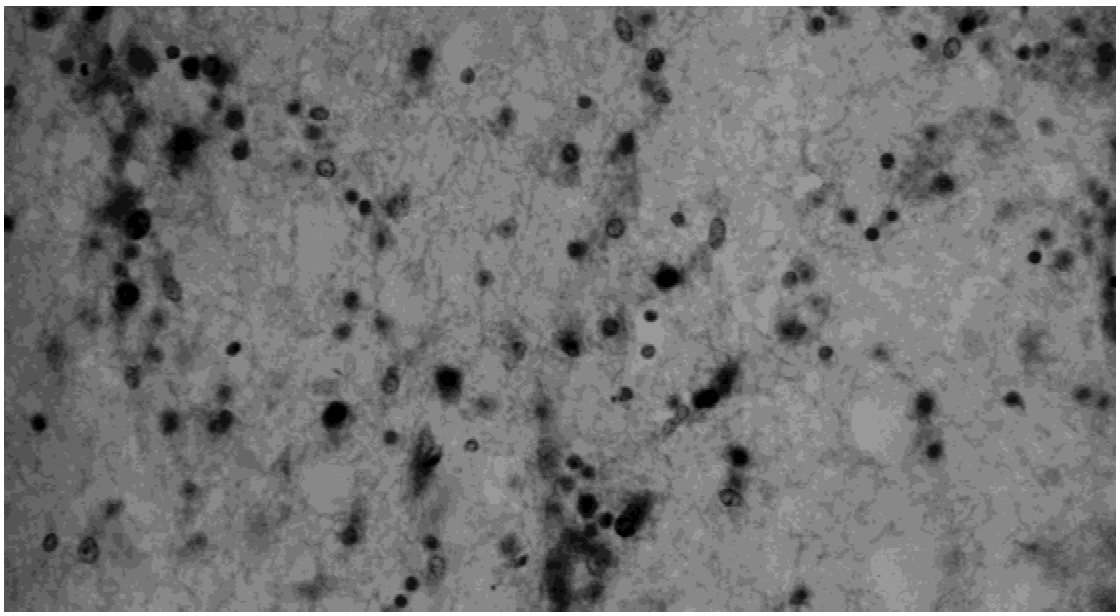

Fig. 3. Detection of human herpes virus-6 DNA in the brain (in situ hybridization; 50×).

al., 1995]. This picture resembles our case and non-GS–related virus infections of the brain [Dietzmann et al., 1989; Kamei et al., 1990], but virus encephalitis has never been proved in GS, though it was suspected, since brain lesions do not respond to broad-spectrum antibiotic treatment.

Evidence links strongly the sixth and seventh members of the family of lymphotropic human herpesviruses, human herpesvirus-6 (HHV-6), and human herpesvirus-7 (HHV-7), both β-herpesviruses, with exanthem subitum (ES, roseola infantum, RI), a common disease of infancy [Yamanishi et al., 1988; Tanaka et al., 1994].

HHV-6 may be considered ubiquitous in the human population, although some epidemiological studies in the past may have used reagents (employed to detect HHV-6 only), which may have cross-reacted with the closely related HHV-7 [Berneman et al., 1993; Ablashi et al., 1995; Di Luca et al., 1995]. Depending on geographic location, seropositivity may be greater than 80% by immunofluorescence assay (IFA) tested anti-HHV-6-IgG antibody titers of >1:20 [Levy et al., 1990; Krueger et al., 1994; Krueger et al., 1995]. After the waning of maternal immunity, extensive dissemination of the virus may occur in man [Saito et al., 1995]. The lymphotropic virus infects almost all children by the age of 2 years usually causing a lifelong latency. Independent of the patient's age HHV-6 infection has been associated with a number of neurologic conditions [Suga et al., 1993], including recurrent febrile seizures and convulsions [Kondo et al., 1993], status epilepticus [Jones et al., 1994], meningitis [Huang et al., 1991], myalgic encephalomyelitis [Wakefield et al., 1989], meningoencephalitis [Ishiguro et al., 1990; Yoshikawa et al., 1992], encephalitis [Asano et al., 1992; Kehl Knox et al., 1992], encephalopathy [Gloning et al., 1991; Asano et al., 1992], multiple sclerosis [Wilborn et al., 1994; Challoner et al., 1995], and chronic fatigue syndrome [Buchwald et al., 1992; Di Luca et al., 1995]. One work group suggests that the central nervous system may be a site of HHV-6 persistence, and that peripheral blood mononuclear cells do not play a role in hibernation of the virus [Caserta et al., 1994]. Herpes virus 6 can be found in postmortem brain tissue [Asano et al., 1990]. Pre- and perinatal infections with lethal outcome or severe residual encephalopathy due to human herpesvirus 6 have been described [Aubin et al., 1992; Wiersbitzky et al., 1993]. In pediatric AIDS patients, human herpesvirus-6 DNA was found in various neurons, numerous oligodendrocytes of the white matter and less frequently in astrocytes, macrophages, and microglia [Saito et al., 1995]. Recent results suggest that lytic infection of astrocytes may play a role in central nervous system (CNS) involvement during acute HHV-6 infection [He et al., 1996]. In absence of an intact immune system, the virus seems to somehow be involved in the process of demyelination [Drobyski et al., 1994; Wilborn et al., 1994; Challoner et al., 1995; Kehl Knox et al., 1995]. It is remarkable that (radiologically) in GS demyelination seems to be a common CNS affection [Brismar and Harfi 1992; Harfi et al., 1992]. In our case we did not find demyelination but neuronal and glial necroses, as well as an extraordinary lymphohistiocytic infiltrate in the neuropil. The picture differs from that in children with HHV-6–associated AIDS encephalopathy [Saito et al., 1995]. Although virus-induced apoptosis may to some extent take place in HHV-6 infection [Krueger et al., 1995], in our GS patient the CNS lesions may have been mediated by T-lymphocytes: CD 8 cells were found to be adjacent to anti-H-AR 3 positive cell detritus (Fig. 4).

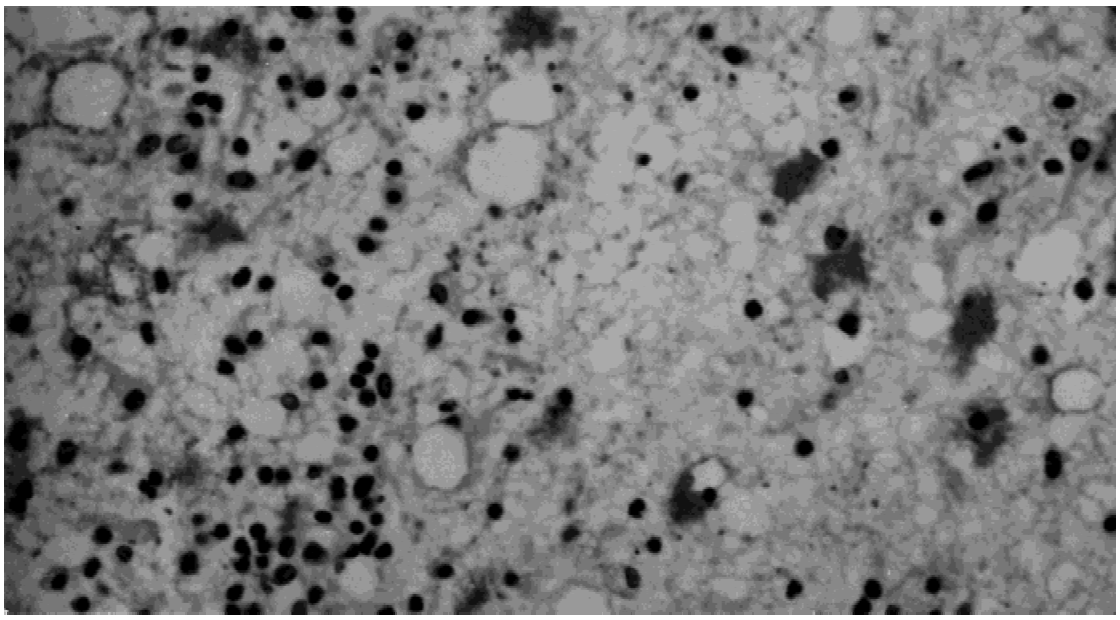

Fig. 4. Immunohistochemistry for human herpes virus-6, late antigen H-AR 3 in the brain (Anti-H-AR3; APAAP; 100×).

Neither cytolytic effects due to HHV-6 nor virus-induced apoptosis alone could cause such lesions.

Active virus replication was not responsible for the CNS lesions seen in our GS patient, because 1) anti-HHV-6-IgM was negative (with an anti-HHV-6-IgG titer positive in the mother and child), 2) immunostaining of brain tissue did not detect replication dependent p41-antigen, and 3) H-AR 3 (which was positive in most lesions examined) is a late antigen in HHV-6 infection. It is noteworthy that ISH does not provide information on the state of viral activity.

There may be doubts whether in our case HHV-6 was the only causative agent for the subacute encephalitis. HHV-6 genes like DR7, U16 (EFLF2, I E-B), U 27 (EPLF 1), U 42, U 89 (pRF3/4, RF2), and U 94 (HCLF2) [Gompels et al., 1995] are known to be able to transactivate various other viruses such as HIV 1, HPV, HHV-7, or EBV [Ensoli et al., 1989; Schonnebeck et al., 1991; Chen et al., 1994; Ablashi et al., 1995; Asano et al., 1995]. In our case PCR antigen detection in stool probes, and/or serology, were positive for CMV, adenovirus, and Coxsackie B1, B2, and B4 virus. Although products of the HHV-6 genes described above may pave the way for one or more of these infectious agents to co-cause encephalitis, immunostainings for CMV, adenovirus, and Coxsackie B1, B2, and B4 antigens in the brain were negative. Anti-Coxsackie-B1 IgG titers found in the child may be due to maternal antibody status, since she was also positive for anti-Coxsackie-B1. Thus positive antibody titers most likely represented a result of immunoglobulin infusions.

The course of events may have taken place as follows: the patient suffered from a human herpesvirus-6 infection of at least the bile duct epithelia in the liver and the CNS. In the latter, excessive H-AR 3 antigen expression was associated with severe CD8 cell-mediated cytotoxic reaction leading to extensive necroses, which were most pronounced in areas of diffuse infiltration.

This is the first report of an HHV-6–associated subacute encephalitis in GS. Further investigations on more patients might show whether virus triggered cytotoxic T-cell reaction is major a causative agent for CNS changes in GS. This is also the first description of GS in a patient of neither Arabic nor Mediterranean ancestry. A patient's ethnic background should thus not be considered to be of any differential diagnostic value.

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